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5-HT and S100β values in evaluating severity of cognitive impairment after traumatic brain injury

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Abstract

Introduction: *The aim of the study was to investigate the relationship between serum serotonin (5-HT) and central nervous system specific protein S100β application value in evaluating the severity of cognitive impairment after traumatic brain injury (TBI).*
Material and methods: *102 patients with TBI treated in Jilin Neuropsychiatric Hospital from June 2018 to October 2020 were selected. According to Montreal Cognitive Assessment (MoCA) scale, patients were tested for cognitive function from multiple levels, such as attention, executive function, memory, and language. Patients with cognitive impairment were included into study group (n = 64), and those without cognitive impairment were assigned to control group (n = 58). Serum 5-HT and S100β were compared between the two groups with β level. Serum 5-HT and S100β were analyzed by receiver operating characteristic curve (ROC), β application value judging cognitive impairment.*
Results: *Serum 5-HT and S100β levels in the study group were significantly higher than those in the control group ($p < 0.05$). In serum 5-HT and S100β, there was a significant negative correlation with a MoCA score ($r = –0.527$, $r = –0.436$; $p < 0.05$, $p < 0.05$). Combined detection of serum 5-HT and S100β's area under ROC curve (AUC) was 0.810 (95% CI: 0.742-0.936, $p < 0.05$), sensitivity was 0.842, and specificity was 0.813.*
Conclusions: *Serum 5-HT and S100β levels are closely related to the cognitive function of TBI patients. Combined detection is helpful to improve the accuracy of predicting cognitive impairment.*

Key words: *traumatic brain injury, serotonin, S100β protein, cognitive impairment, diagnostic efficiency.*

Introduction

Traumatic brain injury (TBI) has a very high mortality and disability rate worldwide [20]. TBI occurs in more than 55 million people all over the world every year, which brings a heavy burden to society and families [3]. According to statistics [16], the probability of cognitive impairment in patients with mild TBI within 3 months of injury is about 50%, while the probability of cognitive impairment in patients with moderate and severe TBI can be as high as 90%, which can lead to different degrees of memory loss, executive ability reduction, language and visual space ability decline, reasoning ability, decreased attention, slow thinking, and other symptoms seriously affecting patient's life, work, and inter-personal skills. At the same time, it increases the burden on patient's family and society, making it difficult for the patient to return to social life and family. More and more evidence show that the history of TBI can significantly increase the risk of developing into a variety of other neurological diseases in later life [15], among which, Alzheimer's disease (AD) is the most common [7,13,14], and seriously affects the effect of rehabilitation training and daily life of patients. Early prediction of the occurrence and severity of cognitive impairment is of great significance to guide clinical practice and improve prognosis of patients [5]. At present, there are two main ways to predict cognitive impairment: Mini-Mental State Exam-

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ination (MMSE) scale and Montreal Cognitive Assessment (MoCA) scale. MMSE examination has short time and good sensitivity, which is easy to be accepted by subjects. It is suitable for screening of large sample population, but its' score is generally high, which is easy to cause missed diagnosis, and is not sensitive to mild cognitive impairment. MoCA scale retains the evaluation of patients' memory, language, and other functions, and increases the items of executive function. It has good sensitivity and specificity for patients with mild cognitive impairment, and is conducive to predict cognitive impairment in patients after TBI. At present, MoCA scale is commonly used to evaluate the cognitive function of patients, with score ranging between 0 and ~30 points. If the score is lower than 26, cognitive impairment is considered. 5-hydroxytryptamine (5-HT) is an important monoamine neuro-transmitter, which mainly plays a role in emotion, learning, memory, arousal, and other activities of human and animal central nervous system as well as regulation of gastro-intestinal motility, secretion, immunity, and other functions [1]. Central nerve specific protein (S100β) belongs to acidic calcium binding protein, which affects differentiation and proliferation of glial cells, promotes formation of synapses after brain injury, and plays an important role in prediction of cognitive impairment and even disease mortality after brain injury [2,8]. The purpose of this study was to investigate serum 5-HT and S100β correlation between protein level and cognitive impairment after brain injury, and to explore its' application value in evaluating the severity of cognitive impairment after TBI, in order to provide reference for clinical early diagnosis and early intervention of cognitive impairment after brain injury.

Material and methods

General information

In total, 102 patients with TBI treated in Jilin Neuropsychiatric Hospital from June 2018 to October 2020 were included into the study. Inclusion criteria were: 1) History of local TBI; 2) MoCA scale successfully completed after waking up in hospital. Exclusion criteria were: 1) Previous cognitive impairment; 2) Patients with brain space occupying lesions or malignant tumors; 3) Coma or vegetative state for more than 14 days after admission; 4) Patients with previous history of brain surgery.

Patients were divided into study group (n = 64) and control group (n = 58). All patients signed informed consent. This study was approved by the hospital's ethics committee.

Research methods

After patient was conscious after admission, cognitive function was evaluated according to MoCA scale, which includes 11 items: attention and concentration, executive function, memory, language, visual structure skills, abstract thinking, calculation, and orientation. The score range is 0~30. If the score is less than 26, cognitive impairment is considered [8]. According to MoCA score, patients in the observation group were divided into four grades: grade I (22 ≤ MoCA score ≤ 25), grade II (19 ≤ MoCA score ≤ 21), grade III (14 ≤ MoCA score ≤ 18), and grade IV (MoCA score < 14).

Then, on empty stomach, 3~5 ml of elbow vein blood was drawn, centrifuged at 3,000 r/min for 15 minutes, and the serum was taken for cryo-preservation. Serum 5-HT and S100β were detected by enzyme-linked immunosorbent assay according to the manufacturer's instruction. 5-HT kit was provided by Guangzhou Wondfo Biotech Co., Ltd. (specification: 25 T/box, 25 servings/box; batch number: W23915106A5-HT), while S100β kit was provided by Shanghai MeiLian Biological Technology Co., Ltd. (Mlbio) (specification: 48 T/box, 48 servings/box; Enzyme-linked assay, batch number: ML057919).

Observation indicators

To compare serum 5-HT and S100β in patients with cognitive impairment of different severity level, the correlation between the two levels and MoCA score was analyzed. Receiver operating characteristic (ROC) curve was applied to evaluate serum 5-HT and S100β, to investigate the effect of cognitive impairment in patients with TBI.

Statistical methods

Statistical software SPSS version 23.0 was used to process the data. Measurement data were expressed in $\overline{X} \pm s$, and t-test was applied for comparison between groups. Counting data were expressed in n (%), and χ^2 inspection was adopted in comparison between groups. ROC working characteristic curve analysis was used to detect serum 5-HT and S100β's application value of judging cognitive impairment in patients with TBI. Area under curve (AUC) > 0.75 was considered good accuracy, and p-value < 0.05 was deemed statistically significant.

Results

Comparison of general data of patients

The study group comprised 39 males and 25 females. The average age was 46.86 ±14.21 years, and body mass index was 23.71 ±3.48 kg/m^2. Trauma sites included left temporal region in 22 cases, right basal ganglia in 28 patients, and posterior occipital region in 14 cases.

Table I. Comparison of general data between two groups ($\bar{x} \pm s$, *n*)

Project	Research group (*n* = 64)	Control group (*n* = 58)	χ^2/t	*P*-value
Gender				
Male	39	31	0.219	0.714
Female	25	27		
Age (years)	46.86 ±14.21	50.81 ±10.12	0.206	0.912
BMI	23.71 ±3.48	21.51 ±2.49	0.422	0.887
Brain injury site				
Temporal region	22	15	6.000	0.159
Basal ganglia region	28	34		
Occipital part	14	9		
Degree of education				
Junior high school or below	17	13	2.492	0.576
High school	29	33		
Bachelor's degree or above	18	19		

Table II. Serum 5-HT and S100β protein in comparison of two groups ($\bar{x} \pm s$, ng/l)

Group	*n*	5-HT	S100β	*t*	*P*-value
Research group	64	87.6 ±9.8	3.07 ±0.27	5.538	0.017
Control group	58	68.2 ±13.2	1.7 ±0.32	4.275	0.003

The control group included 31 males and 27 females. The average age was 50.81 ±10.12 years, and body mass index was 21.51 ±2.49 kg/m^2. Traumatic sites were left temporal region in 15 cases, right basal ganglia in 34 individuals, and posterior occipital region in 9 cases. There was no significant difference between the two groups ($p > 0.05$) (Table I).

Serum 5-HT and S100β in the two groups comparison of protein levels

Serum 5-HT and S100β levels in the study group were significantly higher than those in the control group, and the difference between the two groups was statistically significant ($p < 0.05$) (Table II).

Serum 5-HT and S100β in patients with different severity of cognitive impairment: comparison of protein levels

In the study group, among the 64 TBI patients with cognitive impairment, there were 9 cases of grade I, 21 cases of grade II, 19 cases of grade III, and 15 cases of grade IV. Serum 5-HT and S100β in patients with four severity levels were analyzed, which showed significant differences in protein levels ($p < 0.05$). The severity of cognitive impairment was correlated with serum 5-HT and S100β. The more severe the cognitive impairment, the higher the serum 5-HT and S100β content (Table III).

Table III. Serum 5-HT and S100β in patients with different cognitive impairment severity: comparison of protein levels ($\bar{x} \pm s$, ng/l)

Severity	*n*	5-HT	S100β
Class I	9	60.06 ±5.37	1.64 ±0.31
Class II	21	66.16 ±7.04	1.86 ±0.24
Class III	19	72.48 ±8.36	2.21 ±0.45
Class IV	15	81.23 ±6.22	2.41 ±0.37
F		13.827	12.374
P-value		< 0.001	< 0.001

Serum 5-HT and S100β correlation between protein level and MoCA score

The results of correlation analysis of MoCA score and serum 5-HT and S100β showed that serum 5-HT and S100β had a negative correlation between protein level and MoCA score ($r = –0.527$, $p < 0.05$; $r = –0.436$, $p < 0.05$).

Serum 5-HT and S100β protein levels predict the efficacy of cognitive impairment after traumatic brain injury

Serum 5-HT and S100β protein level was used as the variable test, and whether there was cognitive impairment to draw ROC curve. The results showed that AUC of serum 5-HT level in predicting cognitive impairment in patients with TBI was 0.713 (95% CI: 0.618-0.824,

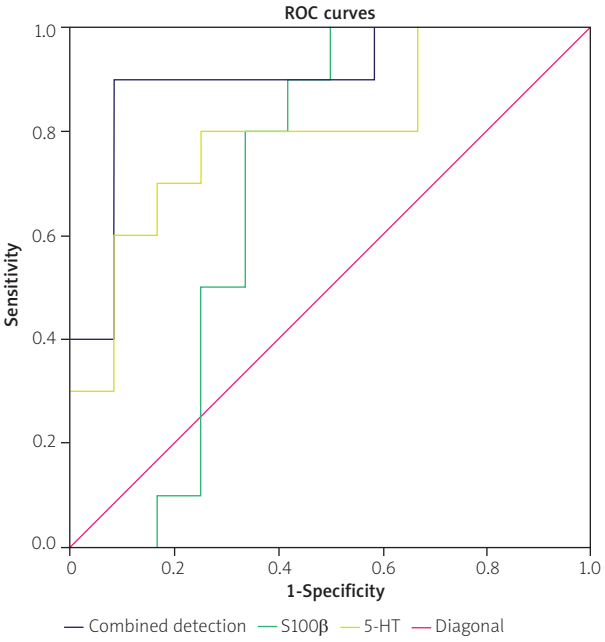

Fig. 1. ROC curves of 5-HT and S100β.

$p < 0.05$), the specificity was 0.634, the sensitivity was 0.812, and the best cut-off value was 73.9 ng/l (Fig. 1).

Serum S100β's AUC of protein level in predicting cognitive impairment in patients with TBI was 0.704 (95% CI: 0.521-0.745, $p < 0.05$), the sensitivity was 0.794, the specificity was 0.512, and the best cut-off value was 1.28 ng/l.

Taking the best cut-off value as the boundary, the parallel diagnostic method was used to detect serum 5-HT, and S100β's AUC of protein level combined prediction of cognitive impairment in patients with TBI was 0.810 (95% CI: 0.742-0.936, $p < 0.05$), the sensitivity was 0.842, and the specificity was 0.813 (Table IV and Fig. 1).

Discussion

The most common complication in patients with TBI is cognitive impairment. The injury mechanism of TBI is complex. Patho-physiological processes, such as post-traumatic neuro-transmitter release, free radical production, calcium-mediated injury, gene activation, mitochondrial dysfunction, inflammatory response, and abnormal coagulation function, can cause secondary injuries, which often lead to adverse outcomes of TBI [12].

In this study, the incidence of cognitive impairment in patients with TBI was 63% (64/102), indicating that the incidence of cognitive impairment in patients with TBI was high, which was similar to that reported by Sharbafshaaer *et al.* [17]. MoCA is a commonly used tool for evaluating cognitive function in clinic, but it has many items and high degree of dependence on patient cooperation, which makes it limited in clinical application [6]. 5-HT is an important monoamine neuro-transmitter, and its' receptor level is correlated with the degree of cognitive impairment after brain injury [19], which can lead to over-excitation of neurons, and 5-HT is released into the blood, increasing its' level in the blood, and further damaging blood-brain barrier, therefore affecting the cognitive function of patients [10]. In this study, by comparing the results of brain injury sites between the study group and the control group, it was found that traumatic brain injury occurred in the temporal and basal ganglia. Studies have shown that patients with brain injury in the brain stem, frontotemporal lobe, and basal ganglia are more likely to have sleep disorders [18]. Sleep disorder can further aggravate cognitive impairment and affect the prognosis of patients.

From the results of this study, the serum 5-HT level in the observation group was significantly higher than that in the control group, and the serum 5-HT level in TBI patients was negatively correlated with MoCA score. Because serum 5-HT is widely distributed in nerves and peripheral tissues, it is also highly expressed in patients with tumor diseases, myocardial hypertrophy, and gastrointestinal diseases, thus, enhancing its' specificity [22].

S100β is an acidic calcium binding protein that exists specifically in central nervous astrocytes, glial cells, microglia, oligodendrocytes, and macroglia, and is easy to be significantly distributed in most sensory nerves and cerebellar nuclei of the brain stem. When brain tissue is damaged, it can participate in the disease through inflammation, calcium overload, and other non-specific ways; therefore, it is considered to be a marker protein of glia. In recent years, clin-

Table IV. Serum 5-HT and S100β efficacy of protein level in predicting cognitive impairment after traumatic brain injury

Index	AUC	95% CI	*P*-value	Truncation value	Jordan index	Sensitivity	Specificity
5-HT	0.713	0.618-0.824	0.002	> 73.9	0.446	0.812	0.634
S100β	0.704	0.521-0.745	0.004	> 1.28	0.306	0.794	0.512
5-HT + S100β joint detection	0.810	0.742-0.936	< 0.001	–	0.655	0.842	0.813

ical scholars have conducted a lot of research on its' pathogenesis in brain injury. Zhang *et al*. [21] analyzed the changes of serum neuron specific enolase (NSE) and S100-β protein and their correlation with cognitive dysfunction in patients with moderate traumatic brain injury (mTBI), and the results showed that there was a good correlation between them. Previous studies confirmed that 96% of S100β is distributed in the brain, so it is considered to be a specific protein of the brain [4]. After cranio-cerebral injury, the injury of brain tissue directly leads to the extensive destruction of brain cells and blood-brain barrier, which makes S100β blood level increased. Due to its' short half-life, its' level decreases rapidly in a short time after injury, but S100β can be caused by delayed dysfunction or continuous apoptosis of glial cells after brain injury overflow, and secondary brain injury can further destroy the blood-brain barrier, with S100β blood level showing secondary increase or sustained high value [9]. Therefore, serum S100β protein level can reflect the degree of central nervous system damage. Studies have shown that the higher the S100β protein level, the higher the risk of cognitive impairment [11].

The results of this study showed that serum S100β protein level in the observation group was significantly higher than that in the control group, and it was negatively correlated with MoCA score; the higher S100β protein level, the more serious cognitive impairment. Serum 5-HT combined with S100β's AUC protein level predicting cognitive impairment in patients with TBI was 0.810. Serum 5-HT and S100β can reflect the causes of cognitive impairment in TBI patients from different aspects, and play a complementary role. Therefore, serum 5-HT and S100β combined with detection of protein level is helpful to improve the accuracy of diagnosing cognitive impairment in patients with TBI. This is of great significance for guiding clinical preventive intervention, especially for patients with cognitive impairment who cannot carry out MoCA score test in time after moderate and severe brain injury.

This study includes several limitations. First, the sample size of this study is too small, and a large-scale research with more participants should be conducted in the future. Secondly, the subjects were not followed up, which affect the accuracy of the study and need further confirmation. In the future, we would carry further investigation and research to enrich the experimental content.

Conclusions

The levels of serum 5-HT and S100β protein in patients with cognitive impairment after TBI are higher. Serum 5-HT and S100β protein level are closely related to cognitive impairment in patients with TBI. The detection of serum 5-HT and S100β level is helpful to evaluate the severity of cognitive impairment and is of great significance for clinical intervention.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Jilin Neuropsychiatric Hospital; all subjects signed the informed consent.

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Disclosure

The authors report no conflict of interest.

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